REMARKS

Applicants thank the Examiner for consideration of the subject patent application. In the Office Action mailed May 8, 2008, Claims 81-84, 86, and 102-103 were pending.

35 U.S.C. § 103

The Examiner has rejected Claims 81-84, 86, and 102-103 under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,352,715 (hereinafter "'715"), in view of U.S. Patent No. 6,365,178 (hereinafter "'178"). The Examiner has also alleged unpatentability under U.S. 103(a) of the presently pending claims over CN 1111987 (" CN '987) in view of the U.S. '178 and the article "Dermal Absorption Models in Toxicology and Pharmacology," ("the article") which was previously submitted by the Applicants. Each of the above described rejections will be discussed in detail below.

Before, discussing each of the above rejections, the Applicant wishes to provide a brief review of the standard required in order to establish a *prima facie* case of obviousness. Specifically, in order to establish a *prima facie* case of obvious three criteria are required for a, namely 1) that the asserted references as modified or combined must teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined must provide a sufficient likelihood of successfully making the modification or combination, and 3) that the Examiner must identify a reason for the modification or combination asserted.

Nothing in the recent *KSR* Supreme Court case changes this basic analysis.

U.S. 715 in view of U.S. '178

The Examiner has asserted that U.S. '715 in combination with U.S. '178 renders the presently pending claims unpatentable. As outlined in the previous office action, U.S. '715 is drawn to a transdermal delivery system for Huperzine A. *See* Abstract. Generally, the '715 reference focuses on pH as a means to increase permeation of the drug and concludes that the only form of huperzine able to penetrate the skin is the neutral form. *See* col. 2, lines 65-67. The '715 reference further speculates that a possible method to further improve delivery of the neutral form of huperzine in liquid reservoir patches is to increase concentration of undissociated huperzine at the huperzine source, by adding non-polar solvents such as alcohols and glycols. *See* col. 8, lines 41-49. Such speculation also comes with the strong caution that, "However, these agents also reduce partitioning of drugs across the skin. Thus, various co-solvents need to be evaluated so as to achieve balance of satisfactory solubility and partitioning." *See* col. 8, lines 49-53. In short, the U.S. 715 actually teaches away from the idea that the co-solvents are used as "permeation enhancers." Specifically, the U.S. 715 explicitly states that "these agents [co-solvents] also reduce partitioning [i.e. permeation]of drugs into the skin." (emphasis added) Further warning that each co-solvent needs to be "evaluated" so that it does not adversely effect permeation of the Hup A. In short, the U.S. '715 not only fails to teach the use of co-solvents **as permeation enhancers**, the reference actually warns against the indiscriminant use of such co-solvents as they can negatively effect permeation of the drug into the skin. As such, '715 teaches away from the present combination asserted by the Examiner.

As the Applicant has raised the issue of teaching away, the Applicant would like to

review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, **a reference will teach away if it suggests** that the **line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Clearly in the present case, a person of ordinary skill in the art is disincentivised from attempting to use any co-solvents to enhance permeation as this is not the expressed reason for their use in the '715 reference to begin with.

Applicants further note that all discussion of the use of co-solvents to alter the permeation of the Huperzine is found exclusively in Example 3, which is a Valia-Chien permeation cell test using donor solutions to deliver the Huperzine. In other words, the test was simulating a liquid reservoir patch and not an adhesive patch. Discussion of testing of huperzine skin permeation using an adhesive patch is found in Example 4, specifically, in Columns 11-13 and includes no discussion relating to the use of permeation enhancers and an adhesive matrix. In fact, U.S. 715 expressly states

that the variation in drug permeation found in the two different adhesive patches tested was "an effect of intrinsic interaction between the adhesive and the drug and not simple (sic) due to formulation factors." (Column 11, lines 64-67)

The Examiner has conceded that the presently claimed blood plasma levels of huperzine are not taught by U.S. '715. However, the Examiner continues to assert that such levels can be readily determined by one having ordinary skill in the art because such levels "are controlled by the amount of the drug included in the system as well as by the ingredients of the transdermal formulation used to deliver the huperzine such as the type of adhesive, the permeation enhancers, and other additives in the formulation." Applicants do not dispute that permeation kinetics, and ultimately blood plasma levels, do correlate, at least in part, to the chemical components of the transdermal formulation. However, Applicants vigorously dispute the Examiner's apparent assertion that the currently claimed blood plasma levels could be readily achieved through simple experimentation or "tinkering" with other transdermal formulations.

As discussed in previous office action responses, transdermal drug delivery is a very complex and delicate art. For example, permeation or penetration enhancers for specific active agents are not easy to identify. The Applicants submit that such teachings regarding the fickle and unpredictable nature of penetration enhancers are generally known in the art. There are numerous examples of third party teachings regarding the difficulty of formulating transdermal matrix patches, and in particular selecting and formulating with permeation enhancers. For example, U.S. Patent No. 5,500,222 which also describes permeation enhancers in the same fashion:

> No "universal" permeation enhancer has been identified. Instead, the behavior of permeation enhancers is highly idiosyncratic; a permeation enhancer effective for one drug may not be effective with other drugs, including closely related drugs.
>
> Often, a permeation enhancer will exacerbate irritation and sensitization problems by allowing high transdermal permeation rates of the drug or permeation enhancer or permitting otherwise impermeable components of the transdermal device to enter the skin. Many potential permeation enhancers interact adversely with other components of transdermal devices. One major problem is that many potential permeation enhancers are not compatible with medically acceptable contact adhesives. Enhancers may improve the transdermal permeation rate adequately, but not adequately reduce the lag time.
>
> The use of a permeation enhancer in any transdermal drug delivery device

> necessarily complicates the design and development of the device. Permeation enhancers cause compatibility problems throughout the delivery system. Instead of having to characterize the properties of the reservoir compositions, adhesives, and release-controlling materials with respect to just the drug, these materials must now have the proper characteristics with respect to both the drug and the permeation enhancer. Typically, drugs and permeation enhancers have very different physical and chemical properties, and, in most cases, the properties of mixtures of the drug with the permeation enhancer are unknown. For example, permeation enhancers can cause, among other problems, cohesive failure of adhesives and can partition through other components in the system. See col. 2, line 47 through col. 3, line 12.

Another similar third party statement regarding the complexity unpredictability of permeation enhancement in the transdermal arts is found in U.S. Patent No. 7,214,381 which states in part:

> To be accepted a permeation enhancer or combination thereof should have the ability to enhance the permeability of the skin for the drug, should be non-toxic, non-irritant and non-sensitizing on repeated exposure.
>
> It is often <u>difficult</u> to predict which compounds will work as permeation enhancers and which permeation enhancers will work for particular drugs. In transdermal drug delivery applications, a compound that enhances the permeability of one drug or a family of drugs may not necessarily enhance the permeability of another drug or family of drugs....
>
> <u>Therefore, the usefulness of a particular compound(s) or mixture thereof as a permeation enhancer must be carefully analyzed and demonstrated by empirical work.</u>

Col. 2, lines 4-20.

Another Example of a related third party teaching regarding the complexity of formulating transdermal compositions with permeation enhancers, particularly with regard to their interaction with other components of the transdermal formulation, can be found in U.S. Patent No 6,267,984 which states:

> In addition to these permeation enhancer-skin interaction considerations, a permeation enhancer must also be evaluated with respect to possible interactions with the transdermal system itself. For example, the permeation enhancer must be

> compatible with the drug to be delivered, the adhesive, and the polymer matrix in which the drug is dispersed. The permeation enhancer should also be selected to ensure suitable balance among tack, adhesion, and cohesive strength of the adhesive.

Col. 2, lines 1-9.

Based on the above teachings regarding the difficulty of formulating transdermal systems and identifying permeation enhancers which can be functional in the transdermal systems, Applicants submit that indiscriminately combining a transdermal system with a permeation enhancer contrary to the knowledge of one of ordinary skill in the art, and in fact, such a practice would not be expected to provide any likelihood of success based on the knowledge of permeation enhancer behavior currently known in the art.

Another example of the difficult nature of transdermal matrix patch formulating can be found in U.S. 715 itself. Two different acrylic pressure sensitive adhesives were chosen as possible candidates for the adhesive in the patch formulation. (Col. 9, lines 58-67). Although the two adhesives were both acrylics, the characteristics of the formulations were very different. For example significant differences existed between the two formulations ability to solubilize the drug (see Table 2), the initial release time for the huperzine (see Table 3), the release rate of the huperzine (see Table 3), the release profiles of the huperzine (see col. 12, lines 38-67 and FIGs 9-10), and the duration of huperzine delivery (*See* FIGs 9-10 and Table 3). Such differences exhibited between two adhesives from the same general chemical family demonstrate another aspect of the difficulty of transdermal matrix patch formulation. Accordingly, the Applicants assert that the Examiner has failed to show a teaching of each and every element of the claim, namely the presently claimed blood plasma levels.

In addition to not teaching the claimed blood plasma levels, the Examiner conceded that U.S. '715 does not teach that "the transdermal device comprises adhesive matrix and specific permeation enhancer." The Examiner relies on U.S. '178 for these teachings. U.S. '178 teaches a method of making a pressure sensitive matrix patch for transdermal delivery of a hydrophilic salt form of a drug. U.S. '178 sets forth a long laundry list of possible drug classes which can be delivered by the pressure sensitive matrix patch. Col. 6, lines 13-31. It further sets forth a broad generic list of possible adhesive polymers which can be delivered. Col. 6, lines 41-55. U.S. '178 goes on to set forth a lengthy laundry list of possible permeation enhancers and/or cell envelope disordering compounds which can be used in the matrix patches, including the broad category of "saturated and unsutarated fatty acids and their esters." The Examiner has cited specifically to Example 11 for the teaching of lauryl lactate as a permeation enhancer. Applicants note that Example 11 is the only location in the entire U.S. '178 patent which mentions any lactic acid ester, including lauryl lactate. Further, Applicants note that Example 11 is drawn to specific formulations for diclofeanc, buspirone, and clonidine, each of which is not only distinct from Huperzine, but is also in a distinct family of drugs far removed from Huperzine. Nothing in U.S. '178 correlates or connects the use of lactic acid esters, or any other permeation enhancer, with Huperzine or any other Anti-Parkinson drug. Based on this, any combination of the teachings of the U.S. '715 and U.S. '178 would require undue experimentation in order to determine which, if any, of the permeation enhancers listed might work.

Further, in light of the above teachings regarding the difficulty of formulating transdermal systems and identifying permeation enhancers which can be functional in the transdermal systems, Applicants submit that indiscriminately combining a transdermal system with a permeation enhancer

contrary to the knowledge of one of ordinary skill in the art, and in fact, such a practice would not be expected to provide any likelihood of success based on the knowledge of permeation enhancer behavior currently known in the art. As such, Applicants submit that, based on the teachings of the '715 reference regarding the detrimental effects of some co-solvents on drug penetration, one skilled in the art would not combine the teachings of the U.S. '715 with U.S. '178 in order to arrive at the presently claimed invention, absent impermissible hindsight reconstruction, particularly in light of the fact that the U.S. '178 reference makes no correlation between any specific active agent and any specific permeation enhancer, let alone huperzine and lauryl lactate.

Additionally, Applicants note that the Examiner is attempting to combine one possible permeation enhancer from a laundry list of permeation enhancers with one specific active agent (i.e. huperzine) even though there is no motivation to choose any specific enhancer and Huperzine is not even directly taught in U.S. '178. In other words, Applicants submit that the one of ordinary skill in the art, upon reviewing the present combination of references, would have no reason to specifically select a fatty acid ester of lactic acid (i.e. lauryl lactate) out of the laundry list of enhancers taught in the U.S. '178 reference and combine it with the transdermal system of the U.S. '715. Therefore, Applicants contend that any such combination would necessarily be based on impermissible hindsight.

As the Applicant has raised the issue of hindsight analysis, the Applicant would like to review the current case law regarding hindsight analysis for the Examiner's convenience. The court has stated that the Applicant's specification cannot be the basis for motivation, i.e., no hindsight reconstruction. Yamonouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 56 U.S.P.Q.2d 1641(Fed. Cir.), reh'g denied, 2000 U.S. App. LEXIS 34047 (2000). Accordingly, if

a prior art reference is sought to provide a specific element of a claim with the use of hindsight, any rejection based thereon is improper and should be withdrawn.

Accordingly, as discussed above, one skilled in the art would not be drawn to, or have reason to believe that a permeation enhancer which works with these drugs would also work with Huperzine. As set forth in above in U.S. Patent No. '381, such a determination would need to "carefully analyzed and demonstrated by empirical work," and therefore would not have been obvious to one skilled in the art.

Accordingly, Applicants submit that the combination of U.S. '715 and U.S. '178 fails to set forth a prima facie case of obviousness. Specifically, the cited references fails to teach the claimed huperzine blood plasma levels, and further the Examiner has failed to demonstrate the reasoning behind why one skilled in the art would make the cited combination and arrive at the presently claimed invention. Such a reason is still required under *KSR*. Therefore, the Applicants assert that the cited references fail to teach each and every element of the pending claims and, therefore, no *prima facie* case of obviousness has bee presented.

CN '987 in view of U.S. 178 and the Article

The Examiner has rejected claims 81-84, 96, and 102-103 under 35 U.S.C. 103(a) as allegedly being unpatentable over CN '987 in view of U.S. '178 and the Article. As discussed in the previous office action, and conceded by the Examiner, the U.S. '987 is directed to a plaster containing Huperzine and azone. See Abstract. Specifically, CN '987 mandates that the formulation include azone (laurocapram) as a permeation enhancer either alone or in combination with another permeation enhancer. In other words, CN '987 teaches that azone is a required permeation enhancer.

As noted by the Examiner, CN '987 does not teach the permeation enhancer presently claimed. In order to remedy the failure of CN '987 to teach the required permeation enhancer the Examiner has relied on U.S. '178 and stated that on skilled in the art would have been motivated to remove the Azone from CN '987 based on the teachings of the Article. Applicants dispute such an assertion.

First, Applicants again remind the Examiner that CN '987 requires azone as a component in the patch and is present in all formulations, even when other permeation enhancing compounds are included. Second, the Examiner's attention is drawn to the above described arguments regarding the difficulty of formulating transdermal matrix patches and selecting permeation enhancers. All arguments set forth above regarding the combination of U.S. '715 with U.S. '178 apply to the present combination of CN '987 and U.S. '178. Instead of repeating the arguments, the Examiner is invited to review the arguments set forth above.

Additionally, the Applicants submit that, even if one skilled in the art would combine CN '987 with the U.S. '178, such a combination would require the use of Azone as a permeation enhancer since CN '987 explicitly mandates the use of Azone, alone or in a combination or mixture with another penetration enhancer as agreed to during the interview. The currently pending claims specifically exclude the use of Azone due to Azone's inability to provide the claimed delivery profile. As such, in order to derive the present invention from the CN '987, alone or in combination with any other reference, one would need to destroy the teachings of the CN '987 reference, namely the inclusion of Azone as a permeation enhancer. As such, the '987 reference, alone or in combination with any reference, cannot render the presently pending claim set obvious.

The Examiner has attempted to overcome the shortcoming of the combination of CN '987 and U.S. '178 by asserting that the Article provides motivation for one skilled in the art to remove

the Azone from CN '987. Applicants note that the present application was filed on November 26, 2003 and is a continuation of U.S. Patent Application Serial No. 09/705,286; filed November 2, 2000, which claims the benefit of U.S. Provisional Application Serial No. 60/163,636; filed on November 4, 1999, and that the Article was published in 2005. Therefore, the Article does not qualify as prior art and cannot be used to reject the presently pending claims. As such, Applicants submit that this rejection is improper and should be withdrawn and the claims allowed.

CONCLUSION

If any impediment remains to further examination of the present application after consideration of the above-recited election and remarks, which could be removed during a telephone interview, the Examiner is invited to telephone the undersigned attorney at (801) 566-6633 so that such issues may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 20-0100.

DATED this 13th day of June, 2008.

Respectfully submitted,

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